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TITLE: Severe Alcoholic Pancreatitis-Associated Acute Lung Injury in Veterans: Risks, Mechanisms, Prediction, and Therapeutic Relevance

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14. ABSTRACT

Background: Acute pancreatitis is a painful, potentially life-threatening condition of the pancreas with an unpredictable course. In this study we hope to identify and propose simple and reliable ways to predict and treat acute pancreatitis.

Hypothesis: Alcohol increases systemic bioavailability of unsaturated fatty acids(UFAs). This, along with the resulting hypocalcemia and hypoalbuminemia worsen cell injury. We propose to test a novel yet simple ratio as a reliable predictor and therapeutic target in the management of alcoholic AP.

Objective: To compare the [Serum free fatty acid/ (Serum calcium x albumin)] ratio as a predictor of severe alcoholic pancreatitis in veterans vs. other classical and proposed predictors.

Methods: Patients admitted with acute pancreatitis are enrolled and laboratory results are recorded. Total of 7 patients and controls have been enrolled to date. Serum samples are obtained and sent to Mayo Clinic, Site 1, for analysis of FFA and circulating dead inflammatory cells. Echocardiogram is done within 24 hours of admission. Control groups include patients who abuse alcohol but do not have pancreatitis and healthy patients. We plan to study the strength of associations of various risk factors for severe acute pancreatitis in comparison to the [Serum free fatty acid/ (Serum calcium x albumin)] ratio.

Conclusion: If our hypothesis is true, it would change the paradigm of managing serum calcium and albumin in acute pancreatitis. This would provide a better, novel yet simple predictor and approach to treatment for severe alcoholic pancreatitis, and potentially acute pancreatitis in general.

15. SUBJECT TERMS

Acute pancreatitis, Severe acute pancreatitis, serum free fatty acids, alcohol pancreatitis, hypocalcemia, hypoalbuminemia

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1. **INTRODUCTION:** This Annual Report details the accomplishments and progress of the first year of CDMRP funding of the project PR151612P1 (Severe Alcoholic Pancreatitis-Associated Acute Lung Injury in Veterans: Risks, Mechanisms, Prediction, and Therapeutic Relevance) from the time period of 9/30/2016-9/29/2017. Acute pancreatitis is a painful, potentially life-threatening condition of the pancreas with a typically abrupt onset and an unpredictable course. In this study, we will identify and propose simple and reliable ways to predict and treat acute pancreatitis. Our central hypothesis is that alcohol increases the systemic bioavailability of unsaturated fatty acids generated from visceral fat lipolysis. This, along with the resulting hypocalcemia and hypoalbuminemia, worsens cell injury, resulting in multisystem organ failure (MSOF) and converting AP to SAP. Our objective is to compare the [Serum free fatty acid/ (Serum calcium x albumin)] ratio as a predictor of severe alcoholic pancreatitis in veterans vs. other classical and proposed predictors, and test it as a therapeutic target.

2. **KEYWORDS:** Acute pancreatitis, Severe acute pancreatitis, serum free fatty acids, alcohol pancreatitis, hypocalcemia, hypoalbuminemia

3. ACCOMPLISHMENTS:

3.1. Goals: As stated in our statement of work (SOW), the first-year goals included first to obtain local IRB approval with HRPO to follow. In addition, we were to set up the study with personnel and to organize systems for identification and recruitment of patients. Following the setup, we were to begin recruitment of patients and normal controls

3.2. What was accomplished:

3.2.1. IRB approval: IRB submission was completed in September 2016. IRB approval was finally obtained with notice to proceed notification on January 17, 2017. Our goal as outlined in the statement of work (SOW) was to have IRB approval within 2 months, however due to IRB delay this was achieved in 4 months.

3.2.2. **HRBO approval:** HRPO submission was completed on January 18, 2017 and was approved on April 19, 2017. This resulted in a delay of 4 months compared to our goal outlined in SOW.

3.2.3. **Hiring of Personnel:** SOW Goal was to be achieved within 3 months. This goal was accomplished within that timeline and our statistician, Dr. Richard Gerkin, and research coordinator, Michele (Yogerst) Gutierrez, were hired by January 2017. Ms. Gutierrez took another position in 9/2017 so Gail Farrell was then hired in her place as research coordinator.

3.2.4. **Recruitment of patients and controls**: Enrollment was to be a total of 140 patients by month 12. This was to include 30 controls, 30 patients with alcohol abuse, and 80 with pancreatitis. Since we were not able to start recruitment until April/May 2017, in addition to other factors, we are currently below our recruitment goal. By month 12, which includes 5 months of active recruiting, we have enrolled 3 patients and 4 controls. We recognize that this, even with the short time period for recruitment, is below goal. Barriers to patient recruitment will be discussed later in the report in detail. We are working to improve our processes for identifying potential patients.

3.3. **Opportunities for training and professional development:** Dr. Vela attended Digestive Disease Week 2017 which allowed for knowledge expansion in the field of pancreatology.

3.4. **How were the results disseminated to communities of interest?** Nothing to report

3.5. **Plan for the next reporting period to accomplish goals?**

3.5.1. **Approval agency delay:** Limitations in achieving our goals were first affected by the delay in getting approval from the IRB and HRPO. This delayed the start of recruitment by >6 months. Once we received the notice to proceed from both agencies, we started recruiting immediately. We began to enroll patients and several control subjects. This will not affect our next 2 years and no specific changes need to be made at this time.

3.5.2. **Inability to perform echocardiograms in timely manner:** Echocardiograms are a crucial component to our study. These are to be performed within 24 hours of admission or consent

(for controls). Unfortunately, just 2 months into recruitment the cardiology department lost several echocardiogram technicians and only 1 remained in house. With this limitation, we could no longer schedule control subjects and recruitment of patients was discouraged until they were better staffed. The cardiology department, despite the cooperation of the chief of Cardiology, could not guarantee that the echocardiograms would be performed within 24 hours. This challenge affected not only our study, but the entire hospital and the majority of echocardiograms were outsourced to outside the VA. That arrangement does not work for our study given the timely nature of the echocardiogram. This personnel problem lasted 2-3 months and in September 2017 the department was back to being staffed adequately. During that month, we were aggressive in trying to find and recruit patients. At the end of the month they lost one of the new hire echocardiogram technicians and they are challenged to accommodate our study once again. The Chief of Medicine in our hospital and the Chief of Cardiology are aware of the constraints this puts on the study and they are actively prioritizing the hire of a new technician.

3.5.3. Challenge in identifying potential patients: Over time we have recognized the most efficient ways to identify potential patients. While the emergency department was thought to be a good potential source, we have found the best way to identify patients is through the abnormal lab values. Our partner in the chemistry lab has been diligent in notifying us of high lipase values and these patients are screened to determine if they are eligible for enrollment. In addition to the abnormal lipase values, we have added the elevated ethanol levels to our alerts so that we can identify those patients who qualify in the group with alcohol use but no pancreatitis. Currently I am meeting weekly with my research coordinator to discuss how to improve this process week by week. Dr. Vela, PI, has started to send reminder alerts to colleagues and hospitalists to better identify potential patients early.

4. IMPACT

4.1. Impact on the development of the principal discipline of the project: Dr. Singh, PI at Site 1, and Dr. Vela, PI at site 2 regularly discuss status of project at each site. Dr. Singh, annual

report filed separately, has found that both the end diastolic and end systolic volumes are less in the animals with pancreatitis. This, although abnormal, will result in *normal* ejection fraction percentage. We plan to look at the patients' echocardiograms for this change as well going forward.

4.2. I**mpact on other disciplines:** Nothing to report.

4.3. **Impact on technology transfer:** Nothing to report.

4.4. **Impact on society beyond science and technology:** Nothing to report.

5. CHANGES/PROBLEMS:

5.1. **Changes in approach and reasons for change**:

5.1.1. The main changes in approach that we have developed have been in the way we identify potential patients. As discussed earlier in the report, the communication with the emergency department has not been as fruitful as we had initially surmised. While we are trying to improve the communication with reminders, we are also further developing relationships with the hospitalists and the laboratory to expand our capture potential.

5.1.2. Despite our low number, Dr. Singh and Dr. Vela unblinded results to discuss findings of the circulating dead inflammatory cells evaluation performed by Dr. Singh's group at site 1. It was discovered that one of the controls, who is morbidly obese, diabetic, had a very high number of dead inflammatory cells in circulation. While this is a very interesting finding, it is more likely that the dead inflammatory cells are coming from the obesity and severe diabetes. Because of this severe abnormality this patient is not suited to be a "normal control." With these findings, we amended our exclusion criteria for controls. The additional exclusion criteria now include BMI>35, Cr>1.2, BUN>20, COPD Oxygen Dependent and patients with complications from diabetes, i.e. retinopathy, neuropathy, etc.

5.2. **Actual or anticipated problems or delays and actions or plans to resolve them:**

5.2.1. **Delay in research agency approval:** The longest delay that we encountered this year was in approval of research agencies. This should not result in any further delay.

5.2.2. **Challenges in obtaining echocardiograms within a timely manner:** Discussions to surmount this challenge is ongoing. We are evaluating multiple options including bringing in an outside echo technician for our study. We are working closely with the Chief of Medicine and Chief of Echocardiograms within the VA hospital to find the best way to achieve our goals with the current constraints.

5.2.3. **Challenges in identifying potential patients:** As discussed previously, we have expanded the alert protocol with laboratory services as well as been more aggressive in reminding hospital colleagues to notify us of potential patients. Dr. Vela and research coordinator are meeting weekly specifically to discuss these challenges and how to improve our systems.

5.2.4. **Changes that had a significant impact on expenditures**: There was a 3 month delay in recruitment of research coordinator which resulted in decreased salary expenditure. Low enrollment has also resulted in underspending for echocardiograms and our statistician does not have enough data to analyze yet. As our recruitment increases, we anticipate the spending to increase.

5.3. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**: Nothing to report

5.4. **Significant changes in use or care of human subjects:** Nothing to report

5.5. **Significant changes in use or care of vertebrate animals:** Nothing to report

5.6. **Significant changes in use of biohazards and/or select agents:** Nothing to report

6. PRODUCTS

6.1. **Publications, conference papers, and presentations:** Nothing to report.

6.2. **Journal publications:** Nothing to report.

6.3. **Books or other non-periodical, one-time publications:** Nothing to report.

6.4. **Other publications, conference papers, and presentations.** Nothing to report.

6.5. **Website(s) or other Internet site(s):** Nothing to report.

6.6. **Technologies or techniques:** Nothing to report.

6.7. **Inventions, patent applications, and/or licenses:** Nothing to report.

6.8. **Other Products:** Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.1. **Individuals who have worked on the project:**

7.1.1. PI: Dr. Stacie A. F. Vela. 2 person months. Role: Oversight of project, initial screening of patients, planning, negotiating, quality control, troubleshooting, manuscript preparation, reporting, communicating with DOD.

7.1.2. Research Coordinator: Michele (Yogerst) Gutierrez. 1.46 person months. Patient consent, blood draws, coordination of specimen transport, maintenance of source documents, documentation

7.1.3. Research Coordinator: Gail Farrell 0.4 person months. . Patient consent, blood draws, coordination of specimen transport, maintenance of source documents, documentation

7.2. **Changes in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period:** Nothing to report.

7.3. **Other organizations were involved as partners?**

7.3.1. SITE 1, Mayo clinic Arizona. Co-PI Dr. Vijay Singh. Performing analysis on blood samples sent from VA including free fatty acid analysis and circulating dead inflammatory cell evaluation, collaboration discussions/meetings to discuss coordination of study and results with Dr. Vela..

8. SPECIAL REPORTING REQUIREMENTS

8.1. **COLLABORATIVE AWARDS:** Independent report sent by Dr. Singh

9. APPENDICES: Nothing to report